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## Citation

Isanaka, Sheila, Christopher Duggan, and Wafaie W Fawzi. 2009. "Patterns of Postnatal Growth in HIV-Infected and HIV-Exposed Children." *Nutrition Reviews* 67 (6) (June): 343–359. doi:10.1111/j.1753-4887.2009.00207.x.

## Published Version

doi:10.1111/j.1753-4887.2009.00207.x

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Published in final edited form as:

*Nutr Rev.* 2009 June ; 67(6): 343–359. doi:10.1111/j.1753-4887.2009.00207.x.

## Patterns of postnatal growth in HIV-infected and HIV-exposed children

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### Abstract

HIV infection can contribute to disturbances in both linear growth and weight gain in early childhood, with disturbances often apparent as early as 3 mo of age. There is little evidence for a difference in the early growth of HIV-exposed but uninfected children compared to healthy controls. Owing to the close association of growth with immune function and clinical progression, an understanding of growth patterns may be an important tool to ensure the provision of appropriate care to HIV-infected and exposed children. Timely growth monitoring may be used to improve the clinical course and quality of life of these children.

### Keywords

HIV; child; postnatal growth

### Introduction

The HIV/AIDS pandemic is one of the most important challenges in global health today. In 2007, 33 million people worldwide were estimated to be living with HIV.<sup>1</sup> The epidemic in much of the world has been concentrated among populations most at-risk, such as men who have sex with men, injection drug users, sex workers and their sexual partners. In sub-Saharan Africa, home to more than two out of every three infected people, the HIV/AIDS epidemic has been sustained in the general population and resulted in increased burdens of disease for both women and children. The majority of people living with HIV in sub-Saharan Africa are women, and nearly 90% of children infected with HIV live in this region.<sup>1</sup>

HIV infection in children is generally due to vertical transmission either during the antenatal and perinatal periods or through breastfeeding. Most studies suggest no difference in the birth size of HIV-positive and negative children born to HIV-infected women, as HIV transmission appears to occur late in gestation.<sup>2</sup> Infection can, however, contribute to disturbances in both linear growth and weight gain in early childhood. Growth failure is now recognized as one of the most common manifestations of HIV infection in children, with failure to thrive reported in 20–70% of infected children.<sup>3</sup> Contributing to the onset of immune deficiency and opportunistic infection, impaired growth is a sensitive indicator of morbidity and mortality in HIV-infected children.<sup>4, 5</sup>

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**Conflict of interest:** None declared.

A number of longitudinal studies have now explored the association between HIV and postnatal growth over time and described a variety of disturbed growth patterns. Differences in observed growth patterns may result from underlying differences in the populations studied, including differences in prenatal growth patterns, the availability of anti-retroviral (ARV) therapy, food supplementation or socioeconomic conditions, or from differences in disease manifestation due to virus sub-types, prevalence of sexually transmitted diseases (STD) or nutritional deficiencies.

In this review, we focus on studies that have examined the association of HIV infection or HIV exposure with postnatal growth over time. We review all longitudinal studies conducted to date, summarize the evidence relating HIV infection and HIV exposure to growth in children, and suggest clinical and research implications and priorities.

## Methods

The patterns of postnatal growth are described in three groups of children defined as follows: 1) HIV-infected children, the majority of which are infected perinatally during late pregnancy and delivery or postnatally during breastfeeding. A small proportion of HIV-infection children acquire HIV through other routes, including transfusion with blood or blood products; 2) children exposed to but not infected with HIV; these children, referred to as sero-reverters, are born to HIV-infected mothers but are not HIV-positive themselves; and 3) healthy controls, including children without HIV exposure or infection born to HIV-negative mothers. The impact of HIV infection is evaluated by summarizing differences in postnatal growth in HIV-infected children vs. sero-reverters, and the impact of HIV exposure is evaluated by summarizing differences in sero-reverters vs. healthy controls.

Studies included in this review were identified through a PubMed search of the literature. All papers published from January 1, 1985 to January 1, 2009 were identified by use of the term “HIV” together with the term “child growth.” Inclusion criteria were as follows: 1) outcomes included anthropometric indices/velocity (e.g. height, weight, head circumference, height-for-age, weight-for-age, weight-for-height, body mass index (BMI)) or body composition measures (e.g. triceps skinfold thickness, arm muscle circumference, fat free mass, or body cell mass); 2) “exposure” groups included HIV-infected children, sero-reverters and/or HIV-uninfected children born to HIV-negative mothers; 3) longitudinal design; and 4) publication in the English language. The focus of this review was limited to longitudinal studies in order to describe postnatal growth dynamics associated with HIV infection and HIV exposure over time. Case reports and studies on the effects of antiretroviral treatment were not included.

Papers meeting the inclusion criteria were reviewed to extract information on study design, exposure and outcome measurement methods, statistical techniques, confounding factors and results. The literature cited in papers recovered through the initial PubMed search was also reviewed to supplement the originally identified publications. All relevant studies are summarized by study setting (i.e. economically ‘developed’ countries including the United States, Europe and Australia vs. economically ‘less developed’ countries including those of Latin America, sub-Saharan Africa, and Asia) to facilitate the identification of possibly different patterns of postnatal growth and to separate the confounding effects of differing levels of treatment and care from the exposure of interest. Results are presented separately for the impact of HIV infection (HIV-infected children vs. sero-reverters) and for the impact of HIV exposure (sero-reverters vs. healthy controls) on postnatal growth. Results from studies that include all 3 groups of children are included in both 2-group comparisons. Results from studies describing the postnatal growth of HIV-infected vs. HIV-uninfected

children (without determination of the uninfected child's HIV exposure status) are presented with results on the impact of HIV infection.

### Epidemiological Evidence

The initial PubMed search identified 845 publications, from which 37 were ultimately identified as longitudinal studies that examined the association of HIV infection or exposure with postnatal growth. From the identification of first pediatric case of HIV in the early 1980's to 1990, only 1 study was identified through this review that considered the association between HIV status of children and postnatal growth.<sup>6</sup> The 1990's saw an increase in evidence for an association between HIV status and growth in children, with 24 new research papers published on this issue between 1990 and 2000.<sup>4, 7–29</sup> Many of these early reports were from populations in the United States and Europe. Data on the anthropometric characteristics of HIV-infected and HIV-exposed children in other settings, including sub-Saharan Africa, largely became available only in the latter half of the 1990's.<sup>4, 7, 8, 17, 18</sup>

### Developed countries

**HIV infection and postnatal growth**—Seventeen studies compared the postnatal growth of HIV-infected and HIV-exposed but - uninfected children in developed countries (Table 1). All studies were from the United States or Western Europe and the mean duration of follow-up ranged from 4 mo to 10 years.

**Linear growth**—Of the 13 papers to examine the association of infection status with height, 11 provided supportive evidence of lower height-for-age among HIV-infected children compared to sero-reverters.<sup>9, 12–14, 19, 21, 24, 27, 29–31</sup> In studies in which an association was found and results reported, the difference in height-for-age Z score between HIV-infected children and sero-reverters ranged from  $-0.73$  to  $-0.90$  Z at 12 mo and  $-0.31$  to  $-0.91$  Z at 18 mo after birth. In studies where differences in height (cm) were presented, differences were small and between 1 and 3 cm through 4 ys of age.<sup>12, 21, 30</sup> At 10 ys of age, the European Collaborative Study observed a difference of  $-7.6$  cm in heights of HIV-infected children vs. sero-reverters.<sup>31</sup> Impairment in height-for-age was most often noted within 3–4 mo after birth.<sup>9, 14, 19, 21, 27, 29–31</sup> but also seen at 15 mo.<sup>13</sup> Early differences in height-for-age were found to persist<sup>19, 21, 24, 30</sup> or increase through follow up.<sup>9, 14, 31</sup> HIV-infected children, compared to sero-reverters, were also found to have increased risks of linear growth failure (defined as  $HAZ < -2$ , growth  $< 4$  cm/y or height deceleration of  $> 10\%$ ; 27% vs. 12.8%)<sup>32</sup>, stunting (7/18 vs. 1/29)<sup>29</sup> and failure to thrive (IRR = 3.9).<sup>23</sup> One multi-site study from the United States did not support an association between HIV infection and lower height-for-age 19–21 mo after birth.<sup>15</sup> Similarly, no difference was found in mean height before vs. after HIV sero-conversion in a small group of hemophiliac boys.<sup>25</sup>

**Weight gain**—The same 13 studies evaluated the association of HIV infection with weight-for-age, 10 of which reported significantly lower weight-for-age in HIV-infected children than in sero-reverters.<sup>9, 12–15, 21, 24, 27, 30, 31</sup> In the studies in which an association was found and results reported, the difference in weight-for-age Z score between HIV-infected children and sero-reverters ranged from  $-0.81$  to  $-0.92$  Z at 6 mo,  $-0.55$  to  $-0.91$  Z at 12 mo,  $-0.77$  to  $-0.98$  Z at 18 mo, and  $-0.57$  Z at 24 mo after birth. Differences in weight (kg) were less than  $-1.5$  kg through 4 ys of follow up.<sup>12, 21, 30</sup> Compared to sero-reverters, HIV-infected children were lighter by 0.61 to 0.65 kg at 6 mo, 0.75 kg at 12 mo, 0.63 kg at 24 mo, and 0.71 to 0.90 kg at 48 mo after birth. After 10 ys of follow up, HIV-infected children in the European Collaborative Study were 6.95 kg lighter than sero-reverters.<sup>31</sup> Two smaller studies by Pollack et al<sup>19, 29</sup> did not support a link between HIV

infection and weight, either as median weight, weight-for-age Z or number underweight with 18 mo of follow up, and the ratio of weight to 50<sup>th</sup> centile for age 25 and weight velocity<sup>24</sup> did not differ by HIV infection status in 2 other small studies. Of the 8 papers in which both lower height-for-age and weight-for-age among HIV-infected children were detected and the timing reported, it was common for differences in height and weight to become apparent at the same time.<sup>14, 21, 27, 31</sup> The change in weight, however, was also observed before 9 and after 13, 24, 30 differences in height.

Of the 6 papers in which weight-for-height was evaluated, 5 detected lower weight-for-height among HIV-infected children compared to sero-reverters. The difference in weight-for-height Z score ranged from  $-0.22$  to  $-0.36$  Z at 6 mo,  $-0.01$  to  $-0.08$  Z at 12 mo, and  $-0.58$  to  $-0.70$  Z at 18 mo after birth. McKinney et al<sup>14</sup> did not detect an association between HIV infection and weight-for-length Z score with over 2 yrs of follow up. The timing of observed differences in weight-for-height were concurrent with differences in both weight and height in 2 studies<sup>12, 15</sup> and occurred after such changes in 2 others.<sup>9, 30</sup> In the large European Collaborative Study, significant height-adjusted differences in weight detected at 3 mo after birth did not persist beyond 12 mo.<sup>21</sup> Two studies evaluated the association of HIV infection and BMI and found BMI to be lower in HIV-infected children compared to sero-reverters in the first 6 mo of life.<sup>10, 12</sup>

**Other measures**—No difference in head circumference-for-age was observed in HIV-infected children vs. sero-reverters in 3 of 5 studies that evaluated this outcome.<sup>12, 13, 19, 21, 27</sup> An early study from the United States by Miller et al<sup>15</sup> was the only longitudinal analysis examining changes in body composition in HIV-infected children over time. The rates of change in muscle mass, measured by arm muscle circumference and tricep skinfold thickness, were found to be lower in HIV-infected children compared to sero-reverters. The rates of change in arm muscle circumference and tricep skinfold thickness were 2 mm / mo and 0.89 mm / mo lower in HIV-infected children, respectively. A cross-sectional analysis of a follow-up study of hemophiliac boys found no difference in triceps skinfold thickness between HIV-infected and -uninfected boys.<sup>16</sup>

**HIV exposure and postnatal growth**—There is less evidence on the association between HIV exposure (as opposed to HIV infection) and postnatal growth, with only 7 papers evaluating the growth of HIV-exposed but - uninfected children in developed country settings (Table 2).

**Linear growth**—Four studies examined differences in height-for-age by HIV exposure status. The European Collaborative Study detected no difference in height-for-age between sero-reverters and the reference population,<sup>31</sup> and Ross et al<sup>26</sup> and Pollack et al<sup>19</sup> found no difference in linear growth between sero-reverters and healthy controls. A smaller Italian study observed lower height-for-age in sero-reverters compared to healthy controls, with mean height-for-age Z scores 0.06 Z, 0.26 Z, and 0.46 Z lower in sero-reverters at 6, 12, and 24 mo of age, respectively.<sup>11</sup> Lipman et al<sup>32</sup> reported a greater risk of growth failure (defined as height-for-age Z  $< -2$ , growth  $< 4$  cm/year or height deceleration of  $> 10\%$ ) among sero-reverters compared to the reference population.

**Weight gain**—No study observed a difference in weight gain between HIV-exposed children and healthy controls. The weight-for-height and BMI of sero-reverters were examined by 1 and 2 studies, respectively.<sup>10, 11, 26</sup> In the Italian studies, both weight-for-height and BMI were found to be higher among the sero-reverters in the first few months after birth, but these differences decreased with time. By 4 mo of age, sero-reverters had similar weight-for-height and BMI as healthy controls. Ross et al<sup>26</sup> found no difference in BMI or change in BMI over 36 mo of follow-up.

**Other measures**—The association between HIV exposure and head circumference-for-age Z scores was assessed in 1 study, where no significant difference between sero-reverters and healthy controls was observed.<sup>19</sup>

### Less developed countries

**HIV infection and postnatal growth**—Fifteen studies evaluated the association of HIV infection and postnatal growth in less developed country settings (Table 3). The majority of these reports were from sub-Saharan Africa, with only 3 studies identified from outside of the region. The duration of follow-up ranged from 4 mo to 8 years.

**Linear growth**—Of the 10 studies in which height-for-age was examined, a negative association was consistently detected in all 4<sup>7</sup> 7<sup>8</sup> 17<sup>28</sup> 33<sup>36</sup> but one study.<sup>37</sup> In studies in which an association was found and results reported, height-for-age Z score was lower in HIV-infected children vs. sero-reverters by 0.23 to 1.55 Z at 6 mo, 0.25 to 0.72 Z at 12 mo, 0.44 to 1.53 Z at 18 mo after birth, and 0.68 to 1.53 Z at 24 mo after birth. Differences in height-for-age detected as early as 3 mo of age 7<sup>8</sup> 34 and before 1 y 4<sup>7</sup> 17<sup>33</sup> 35 persisted throughout follow up. HIV infection was also associated with lower gains in length velocity (−2.8 cm / y, 95% CI: −5.0, −0.6) among children 6 to 11 mo of age in Tanzania,<sup>38</sup> and HIV-infected adolescents in Brazil experienced greater decreases in height-for-age Z scores between their first and last measurement under follow-up than expected in the general population.<sup>36</sup>

**Weight gain**—A negative association between HIV infection and weight gain was detected in all 10 studies in which this relationship was evaluated. The difference in weight-for-age Z score ranged from −0.20 to −1.72 Z at 6 mo, −0.17 to −0.87 Z at 12 mo, −0.87 to −1.43 Z at 18 mo and −0.69 to −1.07 Z at 24 mo after birth. HIV infection was also associated with lower yearly gains in weight among children aged 6 to 11 mo (−1.26 kg, 95% CI: −2.53, 0.02) and 12 to 23 mo (−0.59 kg, 95% CI: −1.05, −0.12) at baseline in Tanzania<sup>38</sup> and with an increased risk of growth disturbance, defined as weight-for-age < 5<sup>th</sup> percentile or no weight gain in 3 mo, in Kenya.<sup>22</sup> The decrease in weight-for-age Z score from first to last measurement under follow-up was also larger among HIV-infected adolescents than expected in the general population ( $\Delta$ WAZ: −0.31).<sup>36</sup> Differences in weight-for-age between groups was detected most consistently at the same time as differences in height-for-age,<sup>4</sup> 7<sup>8</sup> 34 though 2 studies observed the change in weight several months before differences in height were apparent.<sup>17</sup> 33

The link between weight-for-height by infection status was inconsistent in the 6 studies that evaluated this outcome. Two studies provide supportive evidence of a negative association between weight-for-height and HIV infection. In these studies, the difference in weight-for-height between HIV-infected children and sero-reverters ranged from −0.22 to −0.92 Z at 6 mo, −0.04 to −0.50 Z at 12 mo, −0.61 to −0.91 Z at 18 mo and −0.27 Z at 24 mo after birth. In both studies, these differences were detected 6 or more months after differences in height- or weight-for age became apparent. Four studies found no difference in weight-for-height in HIV-infected children compared to sero-reverters.<sup>7</sup> 28<sup>34</sup> 37 In 3 of these studies, no difference in weight-for-height was detected, despite significant differences in height-for-age and/or weight-for-age.<sup>7</sup> 28<sup>34</sup>

**Other measures**—One study examined head circumference-for-age and observed smaller head circumferences among HIV-infected children vs. sero-reverters from 3 to 30 mo of age.<sup>7</sup> The relative risk of failure to thrive among HIV-infected children vs. sero-reverters was assessed in 2 studies, with observed relative risks of 2.25 at 1 y and 46.57 at 2 y in Zambia<sup>6</sup> and 4.48 (95% CI: 2.57, 7.81) in South Africa.<sup>18</sup>



**HIV exposure and postnatal growth**—In the 6 studies to evaluate the association between HIV exposure and postnatal growth in less developed country settings, a lack of association was fairly consistent between HIV exposure and height-for-age,<sup>7, 8, 17, 39</sup> weight-for-age,<sup>7, 8, 17, 20, 39</sup> weight-for-height<sup>8</sup> and head circumference-for-age (Table 4).<sup>7</sup> The only exception was 1 study from Kenya in which height-for-age Z scores were found to be significantly lower at 1.5 mo after birth ( $-0.19$  Z vs.  $-0.48$  Z) and weight-for-height Z score greater at 6 mo ( $0.10$  Z vs.  $0.45$  Z) and 18 mo after birth ( $-0.73$  Z vs.  $-0.16$  Z) among sero-reverters compared to children born to HIV-negative mothers.<sup>37</sup>

**Strengths and limitations of studies**—A number of strengths and limitations characterize the existing studies on HIV and postnatal growth. These are discussed below.

**Exposure assessment**—The method and frequency of assessing HIV infection status in children is particularly relevant in the context of less developed countries, where transmission can continue to occur after birth through breastfeeding. In these settings, it is important to use tests for the presence of HIV antibodies (ELISA and Western blot assays) at 15 or 18 mo of age in conjunction with more specific tests for presence of the virus (polymerase chain reaction assays) at younger ages to account for the time-varying nature of infection status owing to such postnatal transmission. Approximately half of the studies conducted in less developed country settings did not describe the such of such methods for exposure assessment nor account for the timing of transmission in the analysis.<sup>6, 7, 17, 18, 20, 22, 33, 34</sup> Only one recent study by Webb et al<sup>35</sup> used information from repeated PCR measures to account for the timing of transmission in the statistical analysis of differences in growth.

Insufficient exposure assessment also limited the interpretation of findings from one study from Zambia. In Makasa et al,<sup>39</sup> infants' infection status was not determined through laboratory methods. Analyses to evaluate the impact of HIV infection were limited to comparisons of postnatal growth by maternal infection status among children who appeared uninfected at the later follow-up and did not allow for explicit differentiation between HIV-infected children and sero-reverters in the analysis.

**Length of follow up**—Most studies evaluated the short-term effects of HIV on postnatal growth. Data beyond two ys of age are limited, and follow-up less than 6 mo found in some studies<sup>9, 10, 39</sup> may not be long enough to capture the complete pattern of change in growth outcomes. Only 2 studies from sub-Saharan Africa report growth beyond 2 ys. In the one study with follow-up from birth, the later effects of HIV on growth were found to be less than those earlier in life,<sup>7</sup> but this result may be due to the lower survival of those most affected. One European cohort found significant weight and height deficits at 10 ys.<sup>31</sup> The 6 studies that enrolled children at older ages may provide some indication of the patterns of growth among HIV-infected and HIV-exposed children later in childhood.<sup>16, 24, 25, 28, 32, 36</sup>

**Sample Size**—Studies often included a small number of subjects and were affected by considerable drop out, limiting the reliability of conclusions at later time points.<sup>27, 37</sup> Ten studies from developed country settings<sup>9, 10, 12, 13, 15, 19, 24, 25, 27, 29</sup> and 8 from less developed countries<sup>6, 7, 18, 20, 28, 34, 37, 38</sup> included approximately 50 or fewer HIV-positive children.

**Choice of comparison group**—Poor growth in children needs to be interpreted in the context of the health, care and social environment. In evaluating the impact of HIV infection, nearly all studies in this review include comparisons of growth patterns between HIV-infected and HIV-exposed but uninfected children. This choice of comparison group

appropriately controls for many of the differences in socioeconomic status and social background that may exist between children of HIV-positive and HIV-negative mothers, although it is unable to separate the effects of HIV infection from social factors. The design of 5 studies additionally allowed for comparison groups to be selected with consideration for other factors that may affect postnatal growth, by matching on maternal age or parity 7· 8· 12 or selecting healthy controls to be formula-fed as were children born to HIV-infected mothers.10· 11

Studies from developed settings were less likely than those from less developed settings to include appropriate healthy, population-based controls; as a result, there are fewer studies that use HIV-uninfected children born to HIV-negative mothers to describe the impact of HIV exposure (not infection) from developed countries (Table 2 and Table 4). Three studies were found to compare the growth of HIV-infected children with ‘HIV-uninfected children,’ where sero-reverters could not be distinguished from healthy controls among the latter.6· 28· 38

**Limited evidence for body composition endpoints**—Information on body composition, including the distribution of fat and lean body mass, of children is important to characterize how the nutritional status of children changes with HIV infection. This review identified only 1 study that has evaluated changes in body composition in HIV-infected children over time.15 The cross-sectional evidence on the relationship between HIV infection and exposure and body composition appears similarly limited.16· 40–43

**Statistical methods**—The study design and repeated measures used in longitudinal studies generally require data analysis methods that account for the correlation in repeated measurements and the increase in variability in weight and height with age. These more advanced models were successfully applied in 12 studies,4· 12· 13· 15· 17· 21· 26· 29–32· 35· 38 but more than half of the reviewed studies did not account for the longitudinal nature of the data.6–11· 14· 19–21· 24· 25· 27· 28· 33· 34· 37· 39· 44 Control for factors that may influence growth was also inconsistent across studies. Potential confounding due to covariates associated with growth, such as birth weight, gestational age, gender, dietary intake and maternal factors, was not controlled for in the majority of studies 6· 9· 10· 13–15· 17· 19· 20· 23· 24· 27· 29· 30· 32–34· 37· 44 but were considered in others.4· 7· 8· 11· 12· 16· 21· 25· 26· 28· 31· 35· 38· 39

## Comments

Taken together, the data available can be used to highlight a number implications for clinical practice, as well as suggest possible mechanisms of HIV-related growth failure. The data suggest that HIV infection is associated with profound and long-lasting defects in weight and height throughout infancy and childhood. The current evidence indicates that differences in growth patterns become apparent by 3 to 4 mo of age, persist and perhaps increase with time. Wasting associated with HIV infection was less common than stunting or underweight. It is possible that HIV-infected children experience nearly proportional declines in both height and weight such that normal weight-for-height is maintained7· 34 or that wasting in HIV-infected children may become apparent only as children become more sick. The data available also reveal no significant differences in the early growth of sero-reverters and healthy controls, suggesting that viral exposure without infection does not affect growth. These patterns of growth faltering were similar across developed and less developed country settings, despite differences in access to supplemental feeding and antiretroviral therapy and other factors including women’s routes of transmission, virus subtypes, and prevalence of STDs, drug use and nutritional deficiencies.



It was common for differences in weight-for-age to become apparent at the same time as differences in height-for-age in both developed and less developed country settings. As weight is more likely to fall off before height in conditions of protein-energy malnutrition, this pattern of concurrent impairment of weight and height could indicate that other mechanisms may underlie HIV-related growth failure. Possible mechanisms include HIV-related disturbances to energy balance,<sup>40, 43, 45–48</sup> gastrointestinal disturbance and malabsorption,<sup>49–52</sup> and neuro-endocrine changes.<sup>28, 53–58</sup> Growth failure also may occur as a direct result of HIV infection, independent of the variety of secondary illnesses that accompany infection.<sup>30, 59–61</sup>

Understanding of the temporal course and mechanisms of growth impairment through future longitudinal study will continue to be important for the early intervention and care of HIV-infected children if impaired growth precedes and contributes to the onset of immune deficiency and opportunistic infection. Further research in a number of specific areas continues to be warranted to broaden and deepen our current understanding of the impact of HIV on postnatal growth. This includes development of evidence on the effect of HIV infection on body composition in children. As noted above, few studies have addressed the association between HIV infection and exposure and body composition in children. These limited studies suggest that HIV-infected children experience a preferential loss of lean body mass compared to fat, similar to that seen in adults.<sup>62</sup> As changes in body composition may be an additional risk factor for disease progression, further study is needed to describe changes in body composition in HIV-infected children over time.

Evaluation of the effect of HIV infection on adolescent growth and development should also remain a research priority. Advances in the management of HIV means that many perinatally infected children reach adolescence. Only a small number of studies, however, have examined the effect of HIV on adolescent growth and pubertal development to date.<sup>41, 63, 64</sup> Given the increasing survival of this population and the limited information on the effect of HIV on growth and development after 4 years of age, more information on how HIV infection may interact with adolescent growth and maturation is needed. Evaluation of the effect of nutritional intervention / supplementation on growth, immune status and disease progression in children is similarly important. The well-known interaction between nutrition and immune function suggests that nutritional interventions may have the potential to limit morbidity and mortality in HIV-infected individuals.<sup>65</sup> The role of micronutrient status on HIV infection has been examined in several trials in adults and children,<sup>66</sup> though more information on the effectiveness of various macronutrient interventions is still required. Finally, evidence on the effect of ARV therapy on growth and body composition in HIV-infected children must continue to be developed and summarized. ARV therapy has improved the virological, immunological and clinical outcomes of HIV-infected children, and studies on its effects on growth are now becoming available.<sup>61, 67, 68</sup> Additional efforts to develop and consolidate information on the effects of such treatment on growth and body composition in the long-term and in less developed country settings are required.

## Conclusion

Poor growth is common among children infected with HIV, and as a contributor to immune dysfunction, it is associated with disease progression and decreased survival. In this review, we aimed to characterize and quantify the effect of HIV infection and exposure on growth in children. There appears to be little difference in the early growth of HIV-exposed but uninfected and healthy controls, however, abnormal growth patterns in HIV-infected children have been documented in both developed and less developed country settings. A variety of disturbed growth patterns have been described, with disturbances in both height and weight among HIV-infected children often apparent as early as 3 mo of age and

increasing with time. Owing to the close association of growth with immune function and clinical progression among HIV-infected children, an understanding of the growth patterns of HIV-infected children may represent an important tool in targeting children for further assessment. Timely growth monitoring may be used to identify those with sub-optimal growth, ensure the provision of appropriate care and treatment to these children, and help improve their clinical course and quality of life.

## Acknowledgments

**Funding:** This study was supported in part by the National Institutes of Health (grants R01 HD048969 and R01 HD043688). Sheila Isanaka was supported by the Berkowitz Fellowship in Public Health Nutrition (Harvard School of Public Health) and the Caroline Cady Hewey Fund (Harvard University).

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Longitudinal studies from developed countries comparing postnatal growth of HIV-infected children vs. children exposed but not infected with HIV

Table 1

Author	Study site	Years	Sample size Sero- reverter <sup>1</sup>	HIV+ HIV+	Length of follow-up	Endpoints <sup>2</sup>	Associations reported <sup>3</sup>	Results	Variables adjusted for
Agostoni et al. (1998)9	Milan, Italy	1985–1995	92	9 early symp- tomatic 18 late symp- tomatic	Birth to 4 mo	$\Delta$ HAZ	$\downarrow$ HAZ at 2 and 4 mo	Early vs. Late vs. SR 2 mo: $-1.55$ vs. $-0.99$ vs. $-0.38$ 4 mo: $-1.38$ vs. $-0.89$ vs. $-0.09$ 2 mo: $-1.49$ vs. $-0.52$ vs. $0.02$ 4 mo: $-1.49$ vs. $-0.67$ vs. $0.24$	None.
Agostoni et al. (1998)10	Milan, Italy	1985–1995	92	9 early symp- tomatic 18 late symp- tomatic	Birth to 6 mo	$\Delta$ BMI	Early symptomatic vs. SR; $\downarrow$ BMI from 1 to 6 mo	Early vs. Late vs. SR 2 mo: $13.9$ vs. $14.6$ vs. $15.7$ 4 mo: $14.5$ vs. $15.6$ vs. $16.7$ 6 mo: $15.2$ vs. $16.2$ vs. $17.3$	None.
Bamji et al. (1996)23	New York City, New York	1986–1994	396	116	Birth to 15 mo (minimum)	Failure to thrive	$\uparrow$ failure to thrive	46.6 % vs. 15.9% IRR = 3.9 [27.2 / 100 child-years (20.4, 35.5) vs. 6.9 / 100 child-years (5.3, 8.9)]	None.
European Collaborative Study (1995) 21	11 sites across Europe	Not specified.	654	123	Birth to 48 mo	$\Delta$ height (cm)	$\downarrow$ height 3 to 48 mo	6 mo: $64.2 \pm 3.5$ vs. $65.8 \pm 3.3$ Adj % deficit: 2.6 (1.7, 3.5) 24 mo: $83.8 \pm 4.7$ vs. $85.8 \pm 3.8$ Adj % deficit: 2.8 (1.8, 3.9) 48 mo: $100.2 \pm 5.4$ vs. $101.9 \pm 4.4$ Adj % deficit: 1.9 (0.4, 3.4)	Center, parity, maternal race, IV drug use, parental care, and



Author	Study site	Years	Sample size Sero- revert <sup>1</sup>	HIV <sup>+</sup>	Length of follow-up	Endpoints <sup>2</sup>	Associations reported <sup>3</sup>	Results	Variables adjusted for
						height velocity (cm/y)	↓ height velocity birth to 12 mo and after 3 y	Symptoms vs. no symptoms vs. SR 6–12 mo: 18.9 ± 4.9 vs. 16.3 ± 4.6 vs. 17.1 ± 4.5 24–36 mo: 7.0 ± 3.8 vs. 9.6 ± 3.3 vs. 8.5 ± 3.6 36–48 mo: 4.4 ± 3.2 vs. 7.0 ± 3.9 vs. 7.5 ± 2.5 6 mo: 6.66 ± 1.23 vs. 7.31 ± 1.07 Adj % deficit: 9.4 (6.8, 12.0) 24 mo: 11.50 ± 1.78 vs. 12.13 ± 1.56 Adj % deficit: 5.5 (2.5, 8.4) 48 mo: 15.54 ± 2.53 vs. 16.44 ± 1.97 Adj % deficit: 5.8 (1.5, 9.9)	child gender and gestational age.
						Δ weight (kg)	↓ weight 3 to 48 mo	Symptoms vs. no symptoms vs. SR 6–12 mo: 4.51 ± 1.74 vs. 4.36 ± 1.68 vs. 4.51 ± 1.41 24–36 mo: 2.08 ± 1.14 vs. 2.74 ± 0.92 vs. 2.57 ± 0.82 36–48 mo: 0.10 ± 1.62 vs. 1.63 ± 1.10 vs. 2.10 ± 1.07	
						weight velocity (kg/y)	↓ weight velocity birth to 6 mo, 12 to 48 mo (symptomatic vs. SR) and 36 to 48 mo (asymptomatic vs. SR)	Symptoms vs. no symptoms vs. SR 6–12 mo: 4.51 ± 1.74 vs. 4.36 ± 1.68 vs. 4.51 ± 1.41 24–36 mo: 2.08 ± 1.14 vs. 2.74 ± 0.92 vs. 2.57 ± 0.82 36–48 mo: 0.10 ± 1.62 vs. 1.63 ± 1.10 vs. 2.10 ± 1.07	
Geffner et al. (1994)27	Los Angeles County, California	-1990	26	27	Birth to 36 mo	Δ HC Δ HAZ	↔ HC ↓ HAZ from birth to 6 mo, 9 to 12 mo	Not reported. Not reported.	None.
						Δ WAZ	↓ WAZ from birth to 9 mo, 15 to 18 mo		
						Δ HCZ	↓ HCZ from 3 to 9 mo, 12 to 15 mo, 18 to 21 mo Becoming symptomatic during 36 mo vs. SR:		

Author	Study site	Years	Sample size		Length of follow-up	Endpoints <sup>2</sup>	Associations reported <sup>3</sup>	Results	Variables adjusted for
			Sero-reverter <sup>1</sup>	HIV+					
Gertner et al. (1994) <sup>16</sup>	14 sites in the US	1989–1990	126 <sup>4</sup>	207	1 y (age at enrollment 6y to 19 y)	ΔHAZ	↓ HAZ from birth to 6 mo, 9 to 12 mo, 15 to 21 mo, and 24 to 27 mo		
						ΔWAZ	↓ WAZ from birth to 21 mo, 24 to 27 mo		
						ΔWHZ	↓ HCZ from 3 to 9 mo, 12 to 15 mo, 18 to 21 mo		
						Δ height (cm)	Asymptomatic through 36 mo vs. SR: ↓ HAZ from birth to 6 mo ↔ WAZ		
						ΔTSF (mm)	↓ HCZ from birth to 3 mo		
Lipman et al. (2002) <sup>32</sup>	Mid-Atlantic, USA	Not specified.	86	77	Mean 25 mo (range, 3.5 to 70 mo, mean age at baseline 2y, range birth to 14 y)	ΔHAZ	↓ HAZ	−0.56 ± 1.23 vs. −0.01 ± 1.18	Age, weight and race in TSF model.
						ΔWAZ	↓ WAZ	−0.32 ± 1.24 vs. 0.15 ± 1.24	
						ΔWHZ	↔ WHZ	0.25 ± 0.88 vs. 0.30 ± 1.41	
						Δ height (cm)	↓ height	147.8 vs. 150.8	
						ΔTSF (mm)	↔ TSF	2.40 vs. 2.45	
Matarazzo et al. (1994) <sup>24</sup>	Turin, Italy	1990–1992	37	9 asymp-tomatic	24 mo (median age at baseline 2.6 y, range	height velocity	↓ height velocity between baseline and first annual exam	−0.53 HAZ/y ± 2.77 vs. 0.17 HAZ/y ± 2.06; 5.33 cm/y vs. 5.96 cm/y	
						Growth failure (HAZ < −2, growth < 4 cm/y or > 10% height deceleration)	↑ growth failure	27% vs. 12.8%	None.
						Δ HAZ	Asymptomatic: ↓ HAZ at 0, 1, 2 y	Not reported.	None.
						height velocity	Symptomatic: ↓ HAZ at 0, 1, 2 y		
						height velocity	Asymptomatic: ↓ ht velocity		

Author	Study site	Years	Sample size Sero- revert <sup>1</sup> /HIV+	Length of follow-up	Endpoints <sup>2</sup>	Associations reported <sup>3</sup>	Results	Variables adjusted for
McKinney et al. (1993) <sup>14</sup>	Durham, North Carolina	Not specified.	108	62	Birth to 8y	at 1, 2 y		
						Symptomatic: ↓ ht velocity at 1, 2 y		
						Δ WAZ		
						Asymptomatic: ↔ WAZ at 0, 1, 2 y		
						Symptomatic: ↓ WAZ at 0, 2 y		
						Asymptomatic: ↔ wt velocity at 1, 2 y		
						Symptomatic: ↔ wt velocity at 1, 2 y		
						↓ HAZ at 4 to 24 mo	6 mo: -1.21 vs. -0.65 12 mo: -1.25 vs. -0.45 24 mo: -0.83 vs. -0.28	None.
						Δ WAZ	6 mo: -0.96 vs. -0.04 12 mo: -1.06 vs. -0.15 24 mo: -0.76 vs. -0.19	
						Δ WHZ	6 mo: 0.26 vs. 0.61 12 mo: 0.22 vs. 0.17 24 mo: -0.14 vs. -0.09	
Miller et al. (1993) <sup>15</sup>	Boston, MA	1986–1991	37	52	Birth to first follow up (mean 19 mo for SR, 21 mo for HIV+)	↔ HAZ at 19–21 mo	-0.81 ± 0.19 vs. -0.50 ± 0.16	
						↓ WAZ at 19–21 mo	-0.68 ± 0.16 vs. 0.12 ± 0.18	
						↓ WHZ at 19–21 mo	-0.11 ± 0.20 vs. 0.55 ± 0.16	
						Δ HAZ velocity (Z/mo)	-0.00001 ± 0.005 vs. -0.023 ± 0.03	
						Δ WAZ velocity (Z/mo)	-0.001 ± 0.004 vs. -0.014 ± 0.027	
					Δ WHZ velocity (Z/mo)	↔ rate of WHZ change/ mo	0.0001 ± 0.005 vs. 0.006 ± 0.022	

Author	Study site	Years	Sample size		Length of follow-up	Endpoints <sup>2</sup>	Associations reported <sup>3</sup>	Results	Variables adjusted for
			Sero-reverter <sup>1</sup>	HIV <sup>+</sup>					
Miller et al. (2001) <sup>30</sup>	5 sites in US	1990–1997	439	92	Birth to 5 y	ΔAMC (pctile)	↓ AMC at 19–21 mo	43 ± 6.54 vs. 64.5 ± 5.32	
						Δ AMC velocity	↓ rate of AMC pctile change / mo	0.263 ± 0.296 vs. 2.30 ± 0.712	
						Δ TSF (pctile)	↔ TSF at 19–21 mo	29.6 ± 5.41 vs. 40 ± 4.29	
						Δ TSF velocity	↓ rate of TSF pctile change /mo	−1.088 ± 0.304 vs. −0.202 ± 1.06	
						Δ mean growth curve HAZ	↓ HAZ from 3 mo to 5 y	18 mo.: −1.08 Z difference	None.
						Δ height (cm)	↓ height from 6 mo to 5 y	18 mo.: −3.52 cm difference	
						Δ mean growth curve WAZ	↓ WAZ from 6 mo to 5 y	18 mo.: −0.98 Z difference	
						Δ weight (kg)	↓ weight from 6 mo to 5 y	18 mo.: −1.27 kg difference	
						Δ mean growth curve WHZ	↓ WHZ from 14 mo to 5 y	18 mo.: −0.45 Z difference	
						Δ weight-for-height failure to thrive (WAZ ≤ −2)	↓ weight-for-height from 6 mo to 5 y	3 mo: 20.8 % (12.5, 29.1) vs. 11.0% (8.0, 13.9)	
Moye et al. (1996) <sup>12</sup>	5 sites across the US	1990–1993	223	59	Birth to 18 mo	ΔHAZ	↓ HAZ	2 y: 42.2% vs. 15.7% (12.3, 19.2)	Endpoints at 18 mo
								Boys:	considered
								6 mo: −1.09 ± 1.33 vs. −0.31 ± 1.02	adjustment
								12 mo: −0.98 ± 1.48 vs. −0.25 ± 1.07	for child
								18 mo: −0.66 ± 1.28 vs. −0.16 ± 1.00	gender and prenatal
								Girls:	alcohol,
								6 mo: −0.76 ± 1.14 vs. −0.11 ± 0.94	tobacco or
								12 mo: −0.94 ± 1.15 vs. 0.04 ± 0.93	illicit drug
								18 mo: −0.94 ± 1.32 vs. 0.03 ± 0.92	
								Adj diff at 18 mo: −0.735 Z	

Author	Study site	Years	Sample size Sero- reverted/ HIV+	Length of follow-up	Endpoints <sup>2</sup>	Associations reported <sup>3</sup>	Results	Variables adjusted for
					Δ height (cm)	↓ height	Boys: 6 mo: 64.40 ± 3.32 vs. 66.85 ± 2.86 12 mo: 73.19 ± 3.72 vs. 75.31 ± 2.86 18 mo: 80.13 ± 3.79 vs. 81.95 ± 2.96 Girls: 6 mo: 63.57 ± 3.15 vs. 65.52 ± 2.69 12 mo: 71.35 ± 3.43 vs. 74.25 ± 2.66 18 mo: 77.87 ± 4.12 vs. 80.85 ± 2.83 Adj diff at 18 mo: -2.25 cm	exposure, maternal education and antepartum CD4 count.
					ΔWAZ	↓ WAZ	Boys: 6 mo: -0.77 ± 1.20 vs. 0.04 ± 0.96 12 mo: -0.78 ± 1.24 vs. -0.23 ± 0.96 18 mo: -0.89 ± 1.08 vs. -0.12 ± 1.07 Girls: 6 mo: -0.56 ± 1.23 vs. 0.28 ± 1.02 12 mo: -0.63 ± 1.37 vs. 0.04 ± 1.05 18 mo: -0.42 ± 0.99 vs. 0.39 ± 1.26 Adj diff at 18 mo: -0.612 Z	
					Δ weight (kg)	↓ weight	Boys: 6 mo: 6.94 ± 1.09 vs. 7.84 ± 0.96 12 mo: 9.31 ± 1.25 vs. 9.92 ± 1.01 18 mo: 10.37 ± 1.26 vs. 11.34 ± 1.28 Girls: 6 mo: 6.64 ± 1.14 vs. 7.45 ± 0.95 12 mo: 8.81 ± 1.47 vs. 9.53 ± 1.10 18 mo: 10.29 ± 1.16 vs. 11.22 ± 1.43 Adj diff at 18 mo: -0.71 kg	
					ΔWHZ	↓ WHZ	Boys: 6 mo: 0.01 ± 0.88 vs. 0.23 ± 0.90	

Author	Study site	Years	Sample size Sero- revert <sup>1</sup> HIV <sup>+</sup>	Length of follow-up	Endpoints <sup>2</sup>	Associations reported <sup>3</sup>	Results	Variables adjusted for
							12 mo: $-0.06 \pm 0.92$ vs. $0.02 \pm 0.80$ 18 mo: $-0.56 \pm 0.86$ vs. $0.02 \pm 0.95$ Girls: 6 mo: $0.07 \pm 0.87$ vs. $0.43 \pm 1.02$ 12 mo: $0.15 \pm 1.12$ vs. $0.14 \pm 1.07$ 18 mo: $0.16 \pm 0.66$ vs. $0.54 \pm 1.38$ Adj diff at 18 mo: $-0.255$ Z Boys: 6 mo: $-0.71 \pm 1.00$ vs. $-0.23 \pm 0.90$ 12 mo: $-0.79 \pm 1.06$ vs. $-0.43 \pm 0.89$ 18 mo: $-1.31 \pm 1.15$ vs. $0.42 \pm 1.16$ Girls: 6 mo: $-0.50 \pm 1.22$ vs. $0.19 \pm 1.00$ 12 mo: $-0.79 \pm 1.45$ vs. $-0.09 \pm 1.01$ 18 mo: $-0.82 \pm 0.98$ vs. $0.05 \pm 1.21$ Adj diff at 18 mo: $-0.563$ Z Boys: 6 mo: $42.57 \pm 1.33$ vs. $43.39 \pm 1.24$ 12 mo: $45.86 \pm 1.38$ vs. $46.40 \pm 1.20$ 18 mo: $46.62 \pm 1.45$ vs. $47.84 \pm 1.49$ Girls: 6 mo: $41.62 \pm 0.74$ vs. $42.65 \pm 1.36$ 12 mo: $44.48 \pm 2.01$ vs. $45.45 \pm 1.26$ 18 mo: $46.03 \pm 1.26$ vs. $47.10 \pm 1.49$ Boys: 6 mo: $16.69 \pm 1.61$ vs. $17.50 \pm 1.52$ 12 mo: $17.36 \pm 1.41$ vs. $17.46 \pm 1.23$ 18 mo: $16.25 \pm 1.02$ vs. $16.90 \pm 1.25$ Girls:	
					$\Delta$ HCZ	$\downarrow$ HCZ		
					$\Delta$ HC (cm)	$\downarrow$ HC		
					$\Delta$ BMI	$\downarrow$ BMI from birth to 6 mo		



Author	Study site	Years	Sample size		Length of follow-up	Endpoints <sup>2</sup>	Associations reported <sup>3</sup>	Results	Variables adjusted for
			Sero-reverter <sup>1</sup>	HIV+					
Newell et al (2003) <sup>31</sup>	11 sites across Europe	Not Specified.	1403	184	Birth to 10 y	$\Delta$ mean growth curve HA (cm)	$\downarrow$ predicted ht from 3 mo to 10 y	6 mo: $16.30 \pm 1.73$ vs. $17.27 \pm 1.71$ 12 mo: $17.19 \pm 1.78$ vs. $17.21 \pm 1.60$ 18 mo: $16.94 \pm 0.90$ vs. $17.16 \pm 1.81$	Birth weight, gestational age, gender, age*gender, age*HIV status.
								6 mo: $65.52 \pm 0.19$ vs. $66.46 \pm 0.07$	
								12 mo: $83.72 \pm 0.30$ vs. $85.34 \pm 0.12$	
								48 mo: $99.51 \pm 0.43$ vs. $101.63 \pm 0.18$	
								120 mo: $134.54 \pm 1.32$ vs. $142.08 \pm 1.23$	
								6–12 mo: $15.62 \pm 1.87$ vs. $15.88 \pm 1.26$	
Pasi et al. (1990) <sup>25</sup>	Birmingham, United Kingdom	1981–1986 (seroconversion version)	---	27 <sup>5</sup>	Mean 9.2 y, range 4 to 14 y (mean age 12.8 y, range 6–17 y) After seroconversion : mean 4.5 y (range 2 to 6 y)	$\Delta$ HAZ $\Delta$ weight:50 <sup>th</sup> centile for age	$\downarrow$ predicted wt from 1 mo to 10 y	36–48 mo: $7.12 \pm 1.05$ vs. $7.89 \pm 0.82$ 96–120 mo: $5.42 \pm 0.84$ vs. $6.30 \pm 0.81$	Pre-/post-seroconversion comparison matched on child.
								6 mo: $6.84 \pm 0.07$ vs. $7.45 \pm 0.03$	
								12 mo: $11.68 \pm 0.13$ vs. $12.43 \pm 0.06$	
								48 mo: $15.96 \pm 0.21$ vs. $16.67 \pm 0.10$	
								120 mo: $31.33 \pm 1.23$ vs. $38.28 \pm 1.17$	
								6–12 mo: $4.19 \pm 0.72$ vs. $4.45 \pm 0.56$	
Pasi et al. (1990) <sup>25</sup>	Birmingham, United Kingdom	1981–1986 (seroconversion version)	---	27 <sup>5</sup>	Mean 9.2 y, range 4 to 14 y (mean age 12.8 y, range 6–17 y) After seroconversion : mean 4.5 y (range 2 to 6 y)	$\Delta$ HAZ $\Delta$ weight:50 <sup>th</sup> centile for age	$\leftrightarrow$ HAZ	36–48 mo: $1.96 \pm 0.52$ vs. $2.17 \pm 0.47$ 96–120 mo: $2.95 \pm 1.25$ vs. $4.27 \pm 1.38$	Pre-/post-seroconversion comparison matched on child.
								Not reported.	

Author	Study site	Years	Sample size	Length of follow-up	Endpoints <sup>2</sup>	Associations reported <sup>3</sup>	Results	Variables adjusted for
			Sero- reverted <sup>1</sup>	HIV+				
Pollack et al. (1996) <sup>19</sup>	Not specified	1986–1993	29	18 mo	Birth to 18 mo  ΔHAZ  Δ height (cm)	↓ HAZ  ↓ height	Boys: 6 mo: 64.43 ± 3.03 vs. 65.50 ± 2.65 12 mo: 73.93 ± 2.49 vs. 74.86 ± 1.75 18 mo: 81.00 ± 5.50 vs. 80.42 ± 1.99 Girls: 6 mo: 62.00 ± 3.29 vs. 65.59 ± 3.06 12 mo: 70.25 ± 1.89 vs. 72.96 ± 2.92 18 mo: 77.75 ± 3.33 vs. 80.00 ± 2.97	None.
					ΔWAZ Δ weight (kg)	↔ WAZ ↔ weight	Boys: 6 mo: 7.59 ± 1.06 vs. 7.37 ± 1.12 12 mo: 10.19 ± 1.19 vs. 9.82 ± 0.97 18 mo: 11.81 ± 2.20 vs. 10.86 ± 1.02 Girls: 6 mo: 6.58 ± 0.67 vs. 7.01 ± 0.61 12 mo: 8.35 ± 0.75 vs. 9.32 ± 0.68 18 mo: 9.78 ± 1.15 vs. 10.69 ± 0.84	
Pollack et al. (1997) <sup>29</sup>	New York City, New York	1986–1993	29	18 mo	ΔHCZ Birth to 18 mo ΔHAZ	↔ HCZ ↓ HAZ from 3 to 6 mo	6 mo: -1.34 ± 1.12 vs. -0.36 ± 1.02 12 mo: -1.06 ± 1.12 vs. -0.42 ± 0.91 18 mo: -0.69 ± 1.48 vs. -0.60 ± 0.84 7/18 vs. 1/29	None.
					% stunted height velocity	↑ % stunted ≠ rate of ΔHAZ from birth to 6 mo		
					ΔWAZ	↔ WAZ	6 mo: -0.44 ± 0.99 vs. -0.27 ± 1.11 12 mo: -0.64 ± 1.13 vs. -0.12 ± 0.93 18 mo: -0.37 ± 1.65 vs. -0.22 ± 0.88 3/18 vs. 2/27	
					% underweight	↔ % underweight		

Author	Study site	Years	Sample size		Length of follow-up	Endpoints <sup>2</sup>	Associations reported <sup>3</sup>	Results	Variables adjusted for
			Sero-reverter <sup>1</sup>	HIV+					
Saavedra et al. (1995) <sup>13</sup>	Balti-more, MD	Not specified.	50	59	Birth to 70 mo	weight velocity Δ mean growth curve HAZ Δ mean growth curve WAZ Δ mean growth curve HAZ Δ mean growth curve HAZ	↔ rate of ΔWAZ from birth to 18 mo ↓ HAZ from 15 to 70 mo ↓ WAZ from 36 to 70 mo ↔ HCZ from birth to 36 mo	Not reported.	None.

<sup>1</sup> Sero-reverters (SR) are HIV-uninfected children born to HIV-positive mothers.

<sup>2</sup> HA: height/length-for-age. WA: weight-for-age. WH: weight-for-height. HC: head circumference. BMI: Body mass index. AMC: arm muscle circumference. TSF: triceps skinfold.

<sup>3</sup> Arrow indicates direction of the association for HIV+ children compared to sero-reverters.

<sup>4</sup> Comparison group in this study was comprised of HIV-uninfected children born to HIV-negative mothers.

<sup>5</sup> Comparison group in this study was comprised of same HIV-infected children before sero-conversion.

Longitudinal studies from developed countries comparing postnatal growth of children exposed but not infected with HIV vs. children unexposed to HIV

Table 2

Author	Study site	Years	Sample size		Length of follow-up	Endpoints <sup>2</sup>	Associations reported <sup>3</sup>	Results	Variables adjusted for
			HIV-	Sero-reverted <sup>1</sup>					
Agostoni et al. (1998)11	Milan, Italy	1985–1995	65	92	Birth to 24 mo	ΔHAZ	↓ HAZ 18 to 24 mo	6 mo: $-0.06 \pm 0.95$ vs. $0.00 \pm 0.89$ 12 mo: $-0.02 \pm 0.99$ vs. $0.24 \pm 1.05$ 24 mo: $0.13 \pm 1.10$ vs. $0.59 \pm 0.91$ Adj HAZ diff at 18 mo: $-0.55 (-0.17, -0.92)$	HAZ at 18 mo endpoint adjusted for father's income, parity, maternal drug addiction during pregnancy.
						ΔWAZ	↔ WAZ	6 mo: $0.19 \pm 0.82$ vs. $0.18 \pm 0.79$ 12 mo: $0.10 \pm 1.00$ vs. $0.31 \pm 1.00$ 24 mo: $0.13 \pm 1.03$ vs. $0.34 \pm 1.15$	
						ΔWHZ	↑ WHZ 1 to 3 mo	6 mo: $0.25 \pm 0.85$ vs. $0.15 \pm 0.72$ 12 mo: $0.28 \pm 1.00$ vs. $0.34 \pm 0.86$ 24 mo: $0.17 \pm 0.99$ vs. $0.13 \pm 1.07$	
						Δ BMI	↑ BMI at 1 and 2 mo	2 mo: $15.7$ vs. $15.0$ 4 mo: $16.7$ vs. $16.4$ 6 mo: $17.3$ vs. $17.2$ 12.8% vs. 5%	None.
Lipman et al. (2002)32	Mid-Atlantic, USA	Not specified.	86	77	Mean 25 mo (range, 3.5 to 70 mo, age at baseline range birth to 14 y)	Growth failure (HAZ < -2, growth < 4 cm/y or > 10% height deceleration)	↑ growth failure than expected in reference population		None.
Paul et al. (2005)44	5 sites across the US	1989–1999	----	767	Birth to 24 mo	% stunted % underwt	↑ % stunting than reference ↑ % underweight than reference	32 / 703 = 4.6% 44 / 769 = 5.7%	None.
						% micro-	↔ microcephalic than	14 / 682 = 2.1%	

Author	Study site	Years	Sample size		Length of follow-up	Endpoints <sup>2</sup>	Associations reported <sup>3</sup>	Results	Variables adjusted for
			HIV-	Sero-reverter <sup>1</sup>					
Pollack et al. 1996)19	Not specified.	1986–1993			Birth to 18 mo	encephalic	reference		None.
						ΔHAZ			
						Δ height (cm)	↔ height	Boys:	
								6 mo: 65.50 ± 2.65 vs. 65.69 ± 1.33	
								12 mo: 74.86 ± 1.75 vs. 73.19 ± 1.73	
								18 mo: 80.42 ± 1.99 vs. 79.70 ± 3.12	
								Girls:	
								6 mo: 65.59 ± 3.06 vs. 64.79 ± 1.91	
								12 mo: 72.96 ± 2.92 vs. 71.88 ± 2.25	
								18 mo: 80.00 ± 2.97 vs. 79.64 ± 3.63	
Ross et al. (1995)26	Edinburgh, Scotland	1983–1992	383	85	Birth to 36 mo	ΔWAZ			Maternal height age at delivery smoking during pregnancy, postcode deprivation score, parity, method of feeding, twins, case or control status (controls matched
						Δ weight (kg)	↔ weight	Boys:	
								6 mo: 7.37 ± 1.12 vs. 7.78 ± 0.67	
								12 mo: 9.82 ± 0.97 vs. 10.03 ± 0.85	
								18 mo: 10.86 ± 1.02 vs. 11.57 ± 0.81	
								Girls	
								6 mo: 7.01 ± 0.61 vs. 7.30 ± 0.44	
								12 mo: 9.32 ± 0.68 vs. 9.09 ± 0.45	
								18 mo: 10.69 ± 0.84 vs. 10.76 ± 1.49	
						Δ HAZ	↔ HAZ	10 mo: −0.33 (−0.69, 0.04)	
								36 mo: 0.18 (−0.19, 0.55)	
						height velocity (Z/y)	↔ height velocity	Δ to 4 mo: 1.30 (−0.24, 2.85)	
								Δ after 4 mo: 0.03 (−0.14, 0.20)	
						Δ WAZ	↔ WAZ	10 mo: −0.17 (−0.42, 0.08)	
								36 mo: 0.16 (−0.25, 0.57)	
						weight	↔ weight velocity	Δ to 4 mo: 0.94 (−0.09, 1.97)	

Author	Study site	Years	Sample size		Length of follow-up	Endpoints <sup>2</sup>	Associations reported <sup>3</sup>	Results	Variables adjusted for
			HIV−	Sero-reverter <sup>1</sup>					
						velocity (Z/y)		Δ after 4 mo: 0.006 (−0.14, 0.15)	on parity, age, year of delivery,
						Δ BMI for age	↔ BMI Z	10 mo: 0.03 (−0.23, 0.29)	smoking during pregnancy,
						Z		36 mo: −0.02 (−0.44, 0.40)	hospital, postcode
						BMI velocity (Z/y)	↔ BMI velocity	Δ to 4 mo: 0.37 (−0.93, 1.66)	deprivation score, twins, and ethnic group).
								Δ after 4 mo: −0.06 (−0.25, 0.12)	

<sup>1</sup> Sero-reverters are HIV-uninfected children born to HIV-positive mothers.

<sup>2</sup> HA: height/length-for-age. WA: weight-for-age. WH: weight-for-height. BMI: Body mass index.

<sup>3</sup> Arrow indicates direction of the association for sero-reverters compared to HIV-negative children.



Longitudinal studies from less developed countries comparing postnatal growth of HIV-infected children vs. children exposed but not infected with HIV

Table 3

Author	Study site	Years	Sample size Sero- reverter <sup>f</sup>	HIV+	Length of follow-up	Endpoints <sup>2</sup>	Associations reported <sup>3</sup>	Results	Variables adjusted for
Bailey et al. (1999) <sup>8</sup>	Kinshasa , DRC	1989–1992	191	69	Birth to 20 mo	$\Delta$ HAZ	$\downarrow$ HAZ from 3 to 18 mo	6 mo: $-1.06 \pm 0.14$ vs. $-0.75 \pm 0.06$ 12 mo: $-1.67 \pm 0.16$ vs. $-0.95 \pm 0.07$ 18 mo: $-2.12 \pm 0.27$ vs. $-1.68 \pm 0.09$	Cohorts matched by maternal age and parity.
								6 mo: $-0.59 \pm 0.13$ vs. $-0.10 \pm 0.07$ 12 mo: $-1.86 \pm 0.18$ vs. $-0.99 \pm 0.09$ 18 mo: $-2.25 \pm 0.24$ vs. $-1.25 \pm 0.09$	Child's gender, adenopathy, immune status,
								6 mo: $0.30 \pm 0.13$ vs. $0.58 \pm 0.07$ 12 mo: $-0.87 \pm 0.16$ vs. $-0.37 \pm 0.08$ 18 mo: $-1.34 \pm 0.24$ vs. $-0.43 \pm 0.08$	low CD4/CD8 ratio at 3 mo, diarrhea, fever,
								6 mo: $64.1 \pm 0.40$ vs. $65.2 \pm 0.18$ 12 mo: $70.6 \pm 0.42$ vs. $72.6 \pm 0.20$ 18 mo: $75.0 \pm 0.89$ vs. $76.5 \pm 0.26$	mother's HIV serostatus and clinical stage,
								6 mo: $7.01 \pm 1.32$ vs. $7.53 \pm 0.72$ 12 mo: $7.93 \pm 1.88$ vs. $8.85 \pm 0.95$ 18 mo: $8.43 \pm 2.79$ vs. $9.68 \pm 1.09$	CD4 count at delivery and 12 mo, socio- economic status
								6 mo: $10.91 \pm 0.16$ vs. $11.54 \pm 0.09$ 12 mo: $11.20 \pm 0.21$ vs. $12.15 \pm 0.11$ 18 mo: $11.27 \pm 0.29$ vs. $12.61 \pm 0.01$	stature, partner, age and hemoglobin.
								RR: $2.10$ (95% CI: $1.30 - 3.39$ ) RR: $2.84$ (95% CI: $1.58 - 5.11$ ) RR: $2.56$ (95% CI: $1.63 - 4.03$ )	
								Not reported.	
									Cohorts
Berhane et	Kampala	1990–1992	251	84	Birth to 25 mo	weight-for- height	$\uparrow$ % stunted $\uparrow$ % stunted $\uparrow$ % wasted $\Delta$ mean		

Author	Study site	Years	Sample size		Length of follow-up	Endpoints <sup>2</sup>	Associations reported <sup>3</sup>	Results	Variables adjusted for
			Sero-reverter <sup>1</sup>	HIV+					
al. (1997) <sup>4</sup>	Uganda					growth curve HA $\Delta$ mean growth curve WA	$\downarrow$ WA at 6 mo		matched for maternal age.
Bobat et al. (1998) <sup>18</sup>	Durban, South Africa	1990–1993	93	48	Birth to 18 mo minimum (HIV + mean 28.5 mo and SR 23.6 mo)	Failure to thrive (weight and length below 3 <sup>rd</sup> percentile on > 1 occasion or crossing percentile lines) $\Delta$ HAZ	$\uparrow$ Failure to thrive	RR = 4.48 (25 / 48 vs. 13 / 93, 95% CI: 2.57 – 7.81) IRR = 4.08 per 100 child mo (25 / 1037 vs. 13 / 2197, 95% CI: 2.09 – 8.00)	None.
Bobat et al. (2001) <sup>34</sup>	Durban, South Africa	1990–1993	93	48	Birth to 18 mo minimum (HIV + mean 28.5 mo and SR 23.6 mo)	$\Delta$ HAZ	$\downarrow$ HAZ at 3, 6, and 18 mo	6 mo: $-1.14 \pm 1.38$ vs. $-0.08 \pm 1.40$ 12 mo: $-1.26 \pm 1.50$ vs. $-1.01 \pm 1.36$ 18 mo: $-1.82 \pm 0.61$ vs. $-1.06 \pm 1.11$	None.
						$\Delta$ WAZ	$\downarrow$ WAZ at 3, 6, 9 mo	6 mo: $-0.61 \pm 1.51$ vs. $-0.41 \pm 1.30$ 12 mo: $-0.53 \pm 1.43$ vs. $-0.36 \pm 1.53$ 18 mo: $-0.90 \pm 1.14$ vs. $-0.03 \pm 1.43$	
						$\Delta$ WHZ	$\leftrightarrow$ WHZ	6 mo: $0.34 \pm 1.56$ vs. $0.56 \pm 1.43$ 12 mo: $0.50 \pm 1.04$ vs. $0.54 \pm 1.56$ 18 mo: $0.14 \pm 1.30$ vs. $0.75 \pm 1.62$	
Buonora et al. (2008) <sup>36</sup>	Rio de Janeiro, Brazil	-2003	---	108	Median 8.1 y (range, 1.3 to 14 y)	$\Delta$ HAZ	$\downarrow$ HAZ than general population	$\Delta$ HAZ: $-0.27$	Difference between last and first observations pair matched.
					Median age 12.7 y (range, 10.5 to 19.5 y)	$\Delta$ WAZ	$\downarrow$ WAZ than general population	$\Delta$ WAZ: $-0.31$	
Datta et al.	Nairobi,	1986–1992	130	90	---	Growth	$\uparrow$ growth disturbance	OR = 2.1 (95% CI: 1.2, 3.6)	None.

Author	Study site	Years	Sample size Sero- reverter- <i>I</i> HIV +	Length of follow-up	Endpoints <sup>2</sup>	Associations reported <sup>3</sup>	Results	Variables adjusted for
(1994) 22	Kenya				disturbance (WA < 5 <sup>th</sup> percentile or no weight gain in 3 mo)		76% (68 / 90) vs. 61% (80 / 130)	
Halsey et al. (1990)20	Cité Soleil, Haiti	1986–1988	172	55	Birth to 24 mo	Δ Percent of weight-for-age median	↓ WA at 3, 6 mo and 15 to 21 mo	Not reported.
Henderson et al. (1996)17	Blantyre, Malawi	1989–1990	270	92	Birth to 24 mo	Δ mean growth curve HA	↓ HA from 5 to 24 mo	Not reported.
Hira et al. (1989)6	Lusaka, Zambia	1987	107 <sup>4</sup>	42	Birth to 24 mo	Failure to thrive	↑ Failure to thrive	1 y: OR = 2.25
Leandro-Merhi et al. (2000)33	Campinas, Brazil	1985–1996	53	71	Birth to 24 mo	ΔHAZ	↓ HAZ from 9 to 21 mo	2 y: OR = 46.57
						ΔWAZ	↓ WAZ from 3 to 21 mo	9 mo: -2.46 ± 1.16 vs. -0.91 ± 1.26
						ΔWHZ	↓ WHZ from 3 to 15 mo	15 mo: -2.59 ± 1.46 vs. -1.06 ± 0.96
								21 mo: -2.12 ± 1.48 vs. -0.59 ± 1.19
								9 mo: -2.50 ± 1.35 vs. -0.78 ± 1.07
								15 mo: -2.28 ± 1.38 vs. -0.85 ± 0.85
								21 mo: -1.69 ± 1.46 vs. -0.62 ± 1.10
								9 mo: -0.95 ± 1.17 vs. -0.03 ± 0.99
								15 mo: -0.86 ± 1.06 vs. -0.22 ± 1.04
								21 mo: -0.66 ± 1.25 vs. -0.39 ± 1.07
Lepage et al. (1991)28	Kigali, Rwanda	1984–1987	16 <sup>4</sup>	16	Mean 40 mo (range 27 to 62 mo)	Δ HAZ	↓ HAZ	-2.5 ± 1.4 vs. -0.4 ± 0.8
					weight-for-height percent of the median	↔ weight-for-height percent of the median		Matched on child age, sex, and ethnicity.
					Mean age at			

Author	Study site	Years	Sample size		Length of follow-up	Endpoints <sup>2</sup>	Associations reported <sup>3</sup>	Results	Variables adjusted for
			Sero-reverter <sup>1</sup>	HIV+					
Lepage et al. (1996) <sup>7</sup>	Kigali, Rwanda	1988–1994	140	46	enrollment 6.5 y (range 5 to 12 y) Birth to 48 mo	ΔHAZ	↓ HAZ	Not reported.	Cohorts matched on maternal age and parity. None.
						ΔWAZ	↓ WAZ		
						ΔWHZ	↔ WHZ		
						ΔHCZ	↓ HCZ		
Sherry et al. (2000) <sup>37</sup>	Nairobi, Kenya	1991–1994	155	53	Birth to 21 mo	ΔHAZ	↔ HAZ	Not reported.	
						ΔWHZ	↔ WHZ		
						% stunted	↔ % stunted		
						% wasted	↔ % wasted		
Villamor et al. (2004) <sup>38</sup>	Dar es Salaam, Tanzania	1993–1997	477 <sup>4</sup>	47	12 mo (children aged 6 to 60 mo at baseline)	height	↓ height gain in children 6–11 mo at baseline after 1 year of follow up; ↔ height gain in children 12–23 mo and ≥ 24 mo at baseline	6–11 mo: −2.8 (−5.0, −0.6) 12–23 mo: −1.3 (−2.7, 0.1) ≥ 24 mo: 0.3 (−1.3, 1.8)	Age, maternal, education, hemoglobin, vitamin A supplementation, and interactions for each indicator with age.
						velocity (cm/y)			
Webb et al. (2008) <sup>35</sup>	Dar es Salaam, Tanzania	1995–1997	605	247	Birth to 24 mo	weight	↓ weight gain in children 6–11 mo and 12–23 mo at baseline after 1 year of follow up; ↔ weight gain in children ≥ 24 mo at baseline	6–11 mo: −1.26 (−2.53, 0.02) 12–23 mo: −0.59 (−1.05, −0.12) ≥ 24 mo: −0.05 (−0.61, 0.51)	Primiparity adjusted for among children ≥ 24 mo at baseline.
						velocity (kg/y)			
						Δ HAZ	↓ attained HAZ		
						Δ WHZ	↓ attained WHZ	6 mo: −0.23 (−0.39, −0.09) 12 mo: −0.38 (−0.52, −0.24) 24 mo: −0.68 (−0.84, −0.41)  6 mo: −0.38 (−0.56, −0.20)	Maternal education, age, primiparity, height, CD4 cell count at

Author	Study site	Years	Sample size	Length of follow-up	Endpoints <sup>2</sup>	Associations reported <sup>3</sup>	Results	Variables adjusted for
			Sero-reverter <sup>1</sup>	HIV +				
							12 mo: −0.35 (−0.55, −0.16) 24 mo: −0.63 (−0.95, −0.42)	baseline, infant sex and birth weight.

<sup>1</sup> Sero-reverters (SR) are HIV-uninfected children born to HIV-positive mothers.

<sup>2</sup> HA: height/length-for-age. WA: weight-for-age. WH: weight-for-height. HC: head circumference.

<sup>3</sup> Arrow indicates direction of the association for HIV+ children compared to sero-reverters.

<sup>4</sup> Comparison group in this study was comprised of HIV-uninfected children.

Longitudinal studies in less developed countries comparing postnatal growth of children exposed but not infected with HIV vs. children unexposed to HIV

Table 4

Author	Study site	Years	Sample size	Length of follow-up	Endpoints <sup>2</sup>	Associations reported <sup>3</sup>	Results	Variables adjusted for
			HIV- Sero- reverter <sup>1</sup>					
Bailey et al. (1999)8	Kinshasa, DRC	1989–1990	258	Birth to 20 mo	$\Delta$ HAZ	$\leftrightarrow$ HAZ from birth to 20 mo	6 mo: $-0.75 \pm 0.06$ vs. $-0.55 \pm 0.06$	Cohorts matched by maternal age and parity.
							12 mo: $-0.95 \pm 0.07$ vs. $-0.91 \pm 0.07$	
							18 mo: $-1.68 \pm 0.09$ vs. $-1.57 \pm 0.08$	
					$\Delta$ WAZ	$\leftrightarrow$ WAZ from 3 to 20 mo	6 mo: $-0.10 \pm 0.07$ vs. $-0.09 \pm 0.07$	Child's gender, adenopathy, immune status, low CD4/CD8 ratio at 3
							12 mo: $-0.99 \pm 0.09$ vs. $-1.04 \pm 0.08$	
							18 mo: $-1.25 \pm 0.09$ vs. $-1.25 \pm 0.08$	
					$\Delta$ WHZ	$\leftrightarrow$ WHZ from birth to 20 mo	6 mo: $0.58 \pm 0.07$ vs. $0.38 \pm 0.07$	mo, diarrhea, fever, mother's HIV serostatus and clinical stage, CD4 count at delivery and 12 mo, socioeconomic status, stature, partner, age and hemoglobin.
							12 mo: $-0.37 \pm 0.08$ vs. $-0.46 \pm 0.07$	
							18 mo: $-0.43 \pm 0.08$ vs. $-0.50 \pm 0.07$	
				height (cm)			6 mo: $65.2 \pm 0.18$ vs. $65.6 \pm 0.17$	
							12 mo: $72.6 \pm 0.20$ vs. $72.7 \pm 0.19$	
							18 mo: $76.5 \pm 0.26$ vs. $76.9 \pm 0.24$	
					weight(kg)		6 mo: $7.53 \pm 0.72$ vs. $7.50 \pm 0.72$	
							12 mo: $8.85 \pm 0.95$ vs. $8.79 \pm 0.82$	
							18 mo: $89.68 \pm 1.09$ vs. $9.69 \pm 0.94$	
				weight-for-height			6 mo: $11.54 \pm 0.09$ vs. $11.41 \pm 0.09$	
							12 mo: $12.15 \pm 0.11$ vs. $12.06 \pm 0.09$	
							18 mo: $12.61 \pm 0.01$ vs. $12.57 \pm 0.09$	
Halsey et al. (1990)20	Cité Soleil, Haiti	1986 – 1988	3589	Birth to 24 mo	$\Delta$ Percent of weight-for-age median	$\leftrightarrow$ WA	Not reported.	None.
Henderson et al.	Blantyre, Malawi	1989–1990	686	Birth to 24 mo	$\Delta$ mean growth curve	$\leftrightarrow$ HA	Not reported.	None.



Author	Study site	Years	Sample size HIV- Sero-reverter <sup>1</sup>	Length of follow-up	Endpoints <sup>2</sup>	Associations reported <sup>3</sup>	Results	Variables adjusted for
(1996) <sup>17</sup>					HA Δ mean growth curve WA	↔ WA		
Lepage et al. (1996) <sup>7</sup>	Kigali, Rwanda	1988–1994	207 140	Birth to 48 mo	ΔHAZ ΔWAZ ΔWHZ ΔHCAZ	↔ HAZ through 48 mo ↔ WAZ through 48 mo ↔ WHZ through 48 mo ↔ HCAZ through 48 mo	Not reported.	Cohorts matched on maternal age and parity.
Makasa et al. (2007) <sup>39</sup>	Lusaka, Zambia	2001–2003	184 85 HIV + mothers; child status unknown	Birth to 16 weeks	ΔHAZ	↓ HAZ at 6 weeks only	Adj HAZ difference at 6 wks: -0.37 (-0.74, -0.01)	Maternal parity, height, weight, hemoglobin, duration of exclusive breastfeeding, birth weight / length, milk Na/K ratio (mastitis).
Sherry et al. (2000) <sup>37</sup>	Nairobi, Kenya	1991–1994	139 155	Birth to 21 mo	ΔHAZ	↓ HAZ at 1.5 mo	1.5 mo: -0.19 vs. -0.48	None.
					ΔWHZ	↑ WHZ at 6 and 18 mo	6 mo: 0.10 vs. 0.45 18 mo: -0.73 vs. -0.16	

<sup>1</sup> Sero-reverters are HIV-uninfected children born to HIV-positive mothers.

<sup>2</sup> HA: height/length-for-age. WA: weight-for-age. WH: weight-for-height.

<sup>3</sup> Arrow indicates direction of the association for sero-reverters compared to HIV-negative children.